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REVIEW ARTICLE

Glial-Neuronal Interactions in Alzheimer's Disease: The Potential Role of a 'Cytokine Cycle' in Disease Progression

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The role of glial inflammatory processes in Alzheimer's disease has been highlighted by recent epidemiological work establishing head trauma as an important risk factor, and the use of anti-inflammatory agents as an important ameliorating factor, in this disease. This review advances the hypothesis that chronic activation of glial inflammatory processes, arising from genetic or environmental insults to neurons and accompanied by chronic elaboration of neuroactive glia-derived cytokines and other proteins, sets in motion a *cytokine cycle* of cellular and molecular events with neurodegenerative consequences. In this cycle, interleukin-1 is a key initiating and coordinating agent. Interleukin-1 promotes neuronal synthesis and processing of the β-amyloid precursor protein, thus favoring continuing deposition of β-amyloid, and activates astrocytes and promotes astrocytic synthesis and release of a number of inflammatory and neuroactive molecules. One of these, S100β, is a neurite growth-promoting cytokine that stresses neurons through its trophic actions and fosters neuronal cell dysfunction and death by raising intraneuronal free calcium concentrations. Neuronal injury arising from these cytokine-induced neuronal insults can activate microglia with further overexpression of interleukin-1, thus producing feedback amplification and self-propagation of this cytokine cycle. Additional feedback amplification is provided through other elements of the cycle. Chronic propagation of this cytokine cycle represents a possible mechanism for progression of neurodegenerative changes culminating in Alzheimer's disease.

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Introduction

The neurodegeneration of Alzheimer's disease was once exclusively ascribed to neuronal cell alterations; the accompanying cellular changes in astrocytes and microglia (gliosis) were largely dismissed as mere reactions to the neuronal cell changes. We present here a contrasting proposition in which microglia, astrocytes, and their cytokines (*e.g.*, interleukin-1 [IL-1] and S100β) are active participants in neurodegeneration and, indeed, are key intrinsic components of molecular and cellular cascades that have neurodegenerative consequences. These consequences, as carried to the extreme in Alzheimer's disease, can initiate a chain reaction that leads to further neuronal injury, further amyloid deposition, and to subsequent neuritic β-amyloid plaque formation. Remote (neuronal target area) effects result in the spread of tangle-bearing neurons and neuritic plaques from region to region of cerebral cortex. The importance of chronic inflammatory processes, such as we describe here, in the progressive neurodegeneration of Alzheimer's disease has been underscored by recent epidemiological observations suggesting ameliorating effects of chronic anti-inflammatory therapy on the incidence and progression of Alzheimer's disease (3, 7, 8, 49).

Glial-Neuronal Interactions

Interleukin-1. Peripheral immune-response-generated IL-1 is known to drive a number of acute systemic inflammatory processes. Chronic IL-1 overexpression can become detrimental, thwarting attempts at tissue repair and yielding instead degenerative disease (15). In the central nervous system, microglia-derived (20, 29) IL-1 may orchestrate molecular and cellular cascades (21, 57, 62) that constitute the central nervous system equivalent of injury-induced inflammation and repair processes in the periphery (27, 54).

IL-1 has been shown to manifest a number of trophic and toxic actions on central nervous system cells (54), including both autocrine and paracrine effects potentially important in neurodegeneration. Relevant autocrine effects include promotion of microglial proliferation (17) and of increased microglial expression of IL-1 itself as well as IL-6 (33, 57). Relevant paracrine effects of IL-1 include: *i)* induction of neuronal expression (16, 22) and processing (11) of the β-amyloid precursor protein (β-APP), an injury response molecule (19) that is seminal to the pathophysiology of Alzheimer's disease (60); and *ii)* effects on astrocytes, including promotion of astrocytic activation (21) and upregulation of the astrocyte-derived proteins apolipoprotein E (ApoE) and α_1-antichymotrypsin (14). *In vitro*, low levels of IL-1 enhance neuronal survival (10), while higher levels are toxic (9,68).

S100β. Of particular relevance to neurodegenerative effects is IL-1-induced (62) synthesis of S100β, an astrocyte-derived protein encoded by a gene on chromosome 21 (2). S100β has neuroactive functions that include promotion of neurite outgrowth (32), promotion of neuronal survival *in vivo* (6), and elevation of neuronal cytoplasmic free calcium concentrations (5). Autocrine effects of S100β include stimulation of astrocyte proliferation (58), of alterations in astrocyte morphology (59), and promotion of increases in astrocytic intracellular free calcium concentrations (5). Overexpression of S100β in the brains of transgenic mice results in neuropathological changes (48), suggesting that chronic overexpression of S100β, like chronic overexpression of IL-1, can have neurodegenerative consequences.

A Cytokine Cycle

Acute and long term overexpression of IL-1 is seen in a number of conditions characterized by neurodegenerative sequelae. Head injury, for instance, is followed by acute (within hours) increases in cerebral cortical expression of IL-1 (25). Chronic cerebral cortical overexpression of IL-1 is found in Down's syndrome, Alzheimer's disease (27), and idiopathic epilepsy (28). All of these conditions are further characterized by concomitant overexpression of astrocytic S100β (27, 28, 36, 63) and neuronal or neuritic βAPP (13, 43, 61). These examples suggest that, in analogy to IL-1-driven degeneration in the periphery, acute and chronic overexpression of IL-1 in the brain may drive a series of cellular and molecular events with potentially neurodegenerative consequences. Furthermore, the engendered neuronal cell injury or cell death could result in further microglial activation with further overexpression of IL-1, thus producing feed-back amplification of IL-1 expression and setting in motion a self-sustaining cycle of IL-1-driven cascades with attendant progressive neurodegeneration.

In this cytokine cycle, chronic overexpression of IL-1: *i)* promotes astrocyte activation and upregulates astrocytic expression of S100β, ApoE, and α_1-antichymotrypsin; *ii)* stimulates neuronal synthesis and processing of βAPP; and *iii)* has autocrine effects to activate microglia and to further promote IL-1 expression. Each of these IL-1-induced effects has potentially neurodegenerative consequences (42). Chronic astrocyte activation with overexpression of S100β may tax neurons and lead to their demise in three ways: directly through either *i)* increases in the intracellular concentration of free calcium or *ii)* promotion of the growth of neuronal processes that, coincidentally, necessitates further neuronal expression of βAPP with release of neurotoxic (37) β-amyloid; and indirectly through *iii)* S100β induction of astrocytic nitric oxide synthase activity with release of potentially neurotoxic nitric oxide (30). Because of the neuronal damage and loss resulting from this complex of IL-1-driven events, microglia are further activated with additional increases in IL-1 synthesis and release, thus turning the cycle. IL-1-stimulated increased synthesis and processing of βAPP may tax neurons and favor the release of neurotoxic amyloid peptide fragments and deposition of β-amyloid. Activation of the classical complement pathway by β-amyloid (53), which leads to cell lysis with consequent microglial activation, may provide further feed-back amplification of this cytokine cycle. Processing of βAPP also generates non-amyloidogenic secreted fragments (sAPP) that have been shown to activate microglia with enhanced production of inducible nitric oxide synthase and of IL-1 (4), which could provide additional feedback amplification of the cytokine cycle.

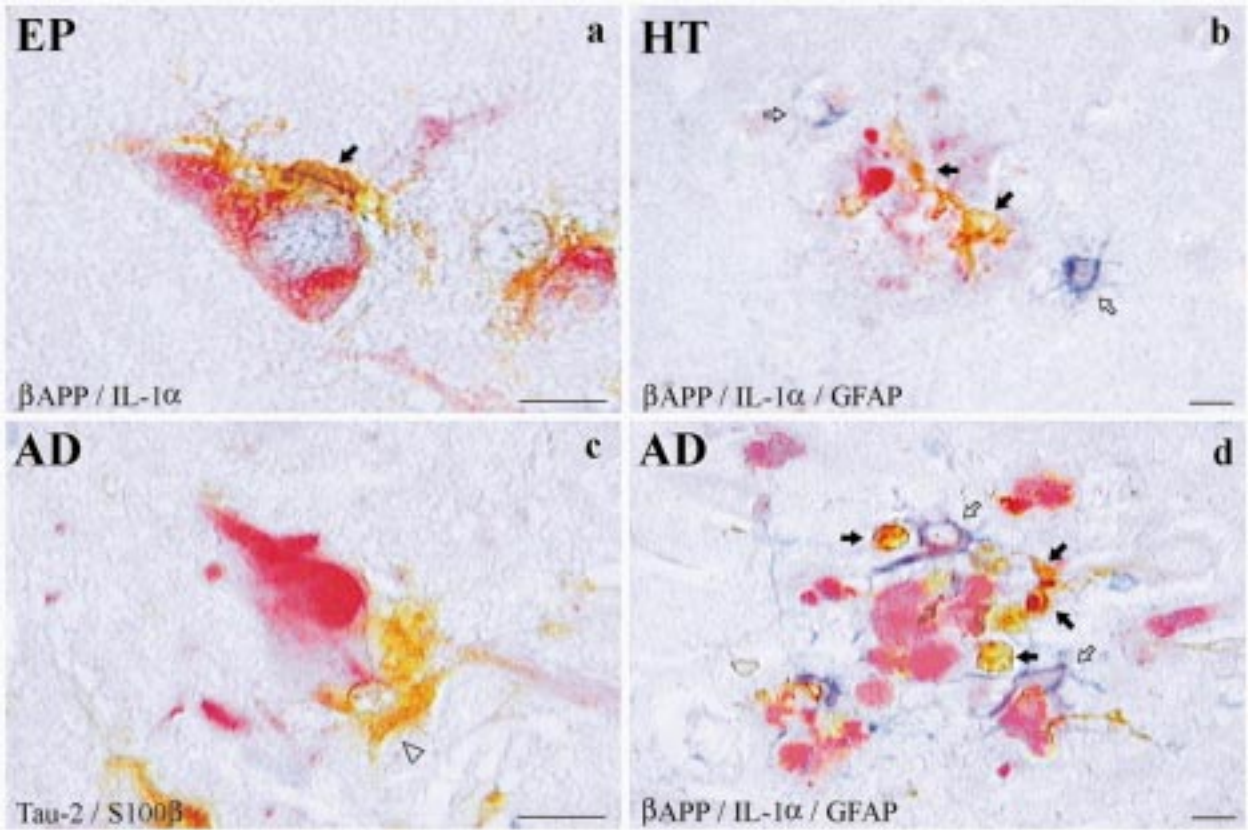

Figure 1. Dual- and triple-immunohistochemical preparations showing glial-neuronal interactions in epilepsy (EP), head trauma (HT), and Alzheimer's disease (AD). a) An activated IL-1α^+ microglial cell (brown, arrow) is present adjacent to a βAPP$^+$ neuron (red) in temporal lobe cortex resected from a patient with intractable complex partial epilepsy. b) Activated IL-1α^+ microglia (brown, solid arrows) and activated GFAP$^+$ astrocytes (blue, open arrows) adjacent to swollen βAPP$^+$ neurites (red) in a 55 year-old patient who died five days following severe head trauma. c) An activated S100β^+ astrocyte (brown, arrow) adjacent to a tau-2$^+$ neuron (red) in an Alzheimer patient. d) A neuritic plaque containing activated IL-1α^+ microglia (brown, solid arrows) and activated GFAP$^+$ astrocytes (blue, open arrows) in association with swollen βAPP$^+$ dystrophic neurites (red) in an Alzheimer patient. Bars = 15 μm.

The Cytokine Cycle in Alzheimer's Disease

Cerebral cortical overexpression of IL-1 is a prominent feature of Alzheimer's disease (12, 26, 27, 64). Both elevated tissue levels of IL-1, and increased numbers of activated, IL-1-immunoreactive (IL-1$^+$) microglia are found in Alzheimer patients. Similar intense, chronic microglial activation with overexpression of IL-1 is observed in Down's syndrome, not only in middle-aged patients with florid Alzheimer-type pathological changes, but also in young and even fetal Down's patients, suggesting that elements of this cytokine cycle are activated years or even decades prior to the onset of clinical symptoms.

Plaque Progression. Activated, IL-1$^+$ microglia in Alzheimer's disease are intimately associated with tangle-bearing (*tau*-immunoreactive) neurons (66) and with amyloid plaques (26) (figure 1). Furthermore, the distribution of activated, IL-1$^+$ microglia among different plaque types, representing stages in a hypothesized sequence (56) of plaque evolution, suggests a role in plaque progression. These microglia are found, in small numbers, in association with most early, "diffuse non-neuritic plaques," suggesting an early role for IL-1 in the evolution of these amyloid deposits into neuritic β-amyloid plaques. They are also found, in greater numbers, in association with virtually all neuritic plaques in Alzheimer's disease. In "diffuse neuritic plaques" (i.e. those neuritic plaques which lack dense β-amyloid cores) they are particularly numerous, while in "dense-core neuritic plaques" (thought to represent a later stage in plaque evolution [56]), these cells are somewhat less abundant. No IL-1$^+$ microglia are found in the "dense core, non-neuritic plaques" that are thought to be the final or "burned-out" stage of β-amyloid plaque evolution. This differential distribution of IL-1$^+$ microglia

among plaque types, together with the established functions of IL-1 noted above, is consistent with an IL-1-driven cascade providing a driving force for plaque evolution and thus for disease progression.

A second cellular component of amyloid plaques in Alzheimer's disease are astrocytes overexpressing biologically active (36) S100β. This astrocyte-derived cytokine manifests neurite growth-promoting properties (32) that have been implicated in the initiation and maintenance of neuritic overgrowth in the amyloid plaques of Alzheimer's disease (36, 43, 63). Among amyloid plaque types, the distribution of activated, S100β$^+$ astrocytes parallels that of activated, IL-1$^+$ microglia (43). These observations, together with our finding that the number of S100β$^+$ astrocytes correlates with the quantity of βAPP$^+$ neurites in individual neuritic plaques (43), suggests that S100β may contribute to both neuritic overgrowth and neuritic overexpression of βAPP in amyloid plaques. These S100β-mediated effects further implicate IL-1-driven cascades in the progression of diffuse amyloid deposits into neuritic plaques in Alzheimer's disease.

IL-1-activated astrocytes also synthesize and release ApoE (14). Extracellular ApoE is present in amyloid plaques in Alzheimer's disease (65, 69), and inheritance of the ApoE ϵ4 allele confers increased risk for development of Alzheimer's disease (69). ApoE has been implicated in the promotion of amyloid aggregation (69) as well as in the growth of dystrophic neurites in amyloid plaques in Alzheimer's disease (65).

Spread of neuropathologic changes. The distribution of activated, cytokine-expressing glia across brain regions in Alzheimer's disease suggests a role for IL-1-driven cascades in promoting the spread of Alzheimer neuropathological changes. The distributions of both IL-1$^+$ microglia and S100β$^+$ astrocytes across brain regions correlates with generally recognized patterns of regional susceptibility in Alzheimer's disease (64, 70). We envision that compromised neurons within an affected brain region manifest axonal and synaptic dysfunctional changes that elicit glial responses in their axonal target areas (*cf* ref 31), which may be located in local environs or in distant brain regions. Such chronic glial activation at sites remote from the original neuronal injury may promote additional neuronal injury, βAPP overexpression, and neuritic alterations; and thus sets in motion a chain reaction through which successive axonal target regions fall victim to the loss of appropriate synaptic connectivity with local glial activation and consequent regional spread of cumulative neuropathological changes.

The Cytokine Cycle in Conditions Predisposing to Alzheimer's Disease or Alzheimer-type Neuropathological Changes

Head injury. A previous history of head injury is a significant environmental risk factor for the subsequent development of Alzheimer's disease (39, 41), and this epidemiological observation is now supported by a variety of neuropathological findings. Boxers who develop dementia pugilistica ("punch-drunk syndrome") exhibit pathological changes that are nearly identical to those seen in Alzheimer's disease, *viz*. large numbers of diffuse β-amyloid plaques and numerous neurofibrillary tangles (50). Even more striking is the observation that diffuse β-amyloid deposits are also found in the brains of approximately 30% of individuals who die shortly after a single severe head injury (51, 52). There is no relationship between presence of these deposits and the presence or distribution of other trauma-associated pathological changes, such as lacerations, contusions, infarcts, or hemorrhages, suggesting that β-amyloid deposition is an independent phenomenon arising in direct response to diffuse mechanical damage (24). Genetic analyses of such trauma victims has now shown over-representation of the ϵ4 allele of the ApoE gene in those head injury patients who develop β-amyloid deposits (45), suggesting a mechanism for the observed synergistic effects of head injury and ApoE genotype in conferring increased risk for Alzheimer's disease (38).

While the association between head injury and Alzheimer's disease is clear, the mechanism underlying this effect is not. There is increased expression of βAPP both in head-injured patients (40) and in experimental models of head injury (1,46), suggesting that head injury may initiate a prolonged overexpression of βAPP which, in susceptible individuals, may ultimately lead to the development of Alzheimer-type neuropathological changes. The most likely stimulus for promoting this increased βAPP expression is IL-1. As discussed above, IL-1 induces excessive expression (16, 22, 62) and processing (11) of βAPP. There is a strong correlation between numbers of βAPP$^+$ neurons and of activated, IL-1$^+$ microglia in head-injured patients and, moreover, there are close spatial relationships between activated, IL-1$^+$ microglia and βAPP$^+$ neurons, and between IL-1$^+$ microglia and βAPP$^+$ dystrophic neurites, the latter clustered in plaque-like structures, found in these head-injured patients (25) (figure 1).

Our studies thus demonstrate fundamental similarities at the molecular level between the acute-phase responses to head injury and the chronic glial responses to Alzheimer's disease. The acute-phase response to

head injury involves upregulation of microglial IL-1 expression and of neuronal βAPP expression, and the appearance of β-amyloid deposits diffusely distributed across cerebral cortical regions in susceptible individuals. This increased expression of βAPP and IL-1 after head injury is presumably part of a protective response. However, such acute overexpression may act as a priming event that confers additional risk for Alzheimer's disease as other risk factors are acquired (*e.g.* age) or expressed (*e.g.* an ApoE ϵ4 allele). Alternatively, levels of these proteins may become chronically elevated, thus initiating a self-sustaining, and pathological, positive feedback cycle that ultimately gives rise to the accumulation of pathological changes characteristic of Alzheimer's disease. Acute head injury may thus be viewed as a model (18) for the early (acute) stages of the more chronic inflammatory processes thought to underlie Alzheimer's disease (42).

Aging. Aging is perhaps the major risk factor for development of Alzheimer's disease, and may represent another priming process. Neurologically intact patients show a progressive increase in brain expression of IL-1 (44) as well as of S100β and S100β mRNA (67). This age-related increase in expression of these two key cycle cytokines, both of which make multiple contributions to the neurodegenerative cascade we propose, may act in synergy with additional risk factors such as head injury and inheritance of an ApoE ϵ4 allele to precipitate the neurodegenerative changes characteristic of Alzheimer's disease.

Epilepsy. Chronic intractable epilepsy is not an established risk for the later development of Alzheimer's disease, but epileptic patients do show accelerated appearance of Alzheimer-type "senile" changes (34). We have shown overexpression of microglial IL-1, astrocytic S100β, and neuronal βAPP in resected temporal lobe tissue from patients with intractable complex partial seizures (28, 61). Neuronal βAPP overexpression is particularly dramatic, appearing in fields of neurons of different sizes, and this overexpression correlates with *i)* increased relative tissue levels of βAPP, *ii)* increased numbers of activated microglia overexpressing IL-1, and *iii)* localization of these activated, IL-1$^+$ microglia adjacent to the βAPP$^+$ neurons (figure 1). It is interesting to note that, as is the case with head injury (45), accelerated "senile" changes are more common and more pronounced in epileptic patients carrying the ApoE ϵ4 allele (23). Chronic glial activation and glial cytokine expression may provide a pathogenic explanation for the increased incidence of "senile" changes observed in patients with chronic epilepsy.

Conclusions

Alzheimer's disease, or Alzheimer-type neuropathological changes, have now been linked to a variety of seemingly diverse genetic and acquired conditions. A common feature of all of these conditions is chronic activation of glial inflammatory processes including microglial overexpression of IL-1, an important pleiotropic acute-phase-response molecule. We propose that IL-1 is the fountainhead of a cycle of molecular and cellular events that have neurodegenerative consequences when chronically overexpressed. This cytokine cycle, activated as an acute response to injury, may have important beneficial functions in protecting or remodeling injured tissue. However, under conditions of chronic or repeated activation, self propagation of this cycle can promote progressive neurodegeneration and, in extreme conditions, a chain reaction involving spread of neurodegeneration across brain regions.

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